function has been shown to attenuate MMP-9 expression (U.S. patent application Serial No. 08/837,201). AP-1 is a heterodimeric protein having two subunits, the gene products of *fos* and *jun*. Antisense compounds targeted to c-*fos* and c-*jun* are described in co-pending U.S. patent application Serial No. 08/837,201, filed March 14, 1997, by Dean *et al.*

[0107] Furthermore, AP-1 is itself activated in certain circumstances by phosphorylation of the Jun subunit at an amino-terminal position by Jun N-terminal kinases (JNKs). Thus, inhibition of one or more JNKs is expected to result in decreased AP-1 activity and, consequentially, reduced MMP expression. Antisense compounds targeted to JNKs are described in co-pending U.S. patent application Serial No. 08/910,629, filed August 13, 1997, by Dean *et al.*

[0108] Infectious diseases of the skin are caused by viral, bacterial or fungal agents. In the case of Lyme disease, the tick borne causative agent thereof, the spirochete *Borrelia burgdorferi*, up-regulates the expression of ICAM-1, VCAM-1 and ELAM-1 on endothelial cells in vitro (Boggemeyer *et al.*, *Cell Adhes. Comm.*, 1994, *2*, 145). Furthermore, it has been proposed that the mediation of the disease by the anti-inflammatory agent prednisolone is due in part to mediation of this up-regulation of adhesion molecules (Hurtenbach *et al.*, *Int. J. Immunopharmac.*, 1996, *18*, 281). Thus, potential targets for therapeutic mediation (or prevention) of Lyme disease include ICAM-1, VCAM-1 and ELAM-1 (*supra*).

[0109] Other infectious disease of the skin which are tractable to treatment using the compositions and methods of the invention include disorders resulting from infection by bacterial, viral or fungal agents (*The Merck Manual of Diagnosis and Therapy*, 15th Ed., pp. 2263-2277, Berkow *et al.*, eds., Rahway, N.J., 1987). With regards to infections of the skin caused by fungal agents, U.S. Patent

5,691,461 provides antisense compounds for inhibiting the growth of *Candida albicans*.

[0110] With regards to infections of the skin caused by viral agents, U.S. Patent 5,166,195, 5,523,389 and 5,591,600 provide oligonucleotide inhibitors of Human Immunodeficiency Virus (HIV). U.S. Patent 5,004,810 provides oligomers capable of hybridizing to herpes simplex virus Vmw65 mRNA and inhibiting its replication. U.S. Patent 5,194,428 and 5,580,767 provide antisense compounds having antiviral activity against influenza virus. U.S. Patent 4,806,463 provides antisense compounds and methods using them to inhibit HTLV-III replication. U.S. Patents 4,689,320, 5,442,049, 5,591,720 and 5,607,923 are directed to antisense compounds as antiviral agents specific to cytomegalovirus (CMV). U.S. Patent 5,242,906 provides antisense compounds useful in the treatment of latent Epstein-Barr virus (EBV) infections. U.S. Patents 5,248,670, 5,514,577 and 5,658,891 provide antisense compounds useful in the treatment of herpes virus infections. U.S. Patents 5,457,189 and 5,681,944 provide antisense compounds useful in the treatment of papilloma virus infections. The antisense compounds disclosed in these patents, which are herein incorporated by reference, may be used with the compositions of the invention to effect prophylactic, palliative or therapeutic relief from diseases caused or exacerbated by the indicated pathogenic agents.

[0111] Antisense oligonucleotides employed in the compositions of the present invention may also be used to determine the nature, function and potential relationship of various genetic components of the body to disease or body states in animals. Heretofore, the function of a gene has been chiefly examined by the construction of loss-of-function mutations in the gene (*i.e.*, "knock-out" mutations) in an animal (*e.g.*, a transgenic mouse). Such tasks are difficult, time-consuming and cannot be

accomplished for genes essential to animal development since the "knock-out" mutation would produce a lethal phenotype. Moreover, the loss-of-function phenotype cannot be transiently introduced during a particular part of the animal's life cycle or disease state; the "knock-out" mutation is always present. "Antisense knockouts," that is, the selective modulation of expression of a gene by antisense oligonucleotides, rather than by direct genetic manipulation, overcomes these limitations (see, for example, Albert *et al.*, *Trends in Pharmacological Sciences*, 1994, *15*, 250). In addition, some genes produce a variety of mRNA transcripts as a result of processes such as alternative splicing; a "knock-out" mutation typically removes all forms of mRNA transcripts produced from such genes and thus cannot be used to examine the biological role of a particular mRNA transcript. Antisense oligonucleotides have been systemically administered to rats in order to study the role of the *N*-methyl-D-aspartate receptor in neuronal death, to mice in order to investigate the biological role of protein kinase C-a, and to rats in order to examine the role of the neuropeptide Y1 receptor in anxiety (Wahlestedt *et al.*, *Nature*, 1993, *363*:260; Dean *et al.*, *Proc. Natl. Acad. Sci. U.S.A.*, 1994, *91*:11762; and Wahlestedt *et al.*, *Science*, 1993, *259*:528, respectively). In instances where complex families of related proteins are being investigated, "antisense knockouts" (*i.e.*, inhibition of a gene by systemic administration of antisense oligonucleotides) may represent the most accurate means for examining a specific member of the family (see, generally, Albert *et al.*, *Trends Pharmacol. Sci.*, 1994, *15*:250). By providing compositions and methods for the simple non-parenteral delivery of oligonucleotides and other nucleic acids, the present invention overcomes these and other shortcomings.

[0112] The administration of therapeutic or pharmaceutical compositions comprising the